

Attorney Docket No.: **MGU-0027**  
Inventors: **Hanrahan and Luo**  
Serial No.: **10/790,273**  
Filing Date: **March 1, 2004**  
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#### **REMARKS**

Claims 7-8 are pending in the instant application. Claims 7 and 8 have been rejected. Claim 7 has been amended. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks.

#### **I. Rejection of Claims Under 35 U.S.C. §112**

Claims 7-8 remain rejected under 35 U.S.C. 112, first paragraph, for failing to meet the enablement requirement. It is suggested that while Applicants amendments to the claims have addressed several issues raised by the Examiner, the issue of tagging an intracellular loop has not been resolved.

Applicants respectfully disagree with this rejection. However, in the interest of facilitating the prosecution of this application, Applicants have amended claim 7 to recite the language that is suggested by the Examiner to be enabled by the disclosure of the instant invention. Support for this embodiment is found at page 15, lines 16-24. Accordingly, the claims as amended meet the requirement of 35 U.S.C. 112, first paragraph, and withdrawal of this rejection is respectfully requested.

#### **II. Rejection of Claims Under 35 U.S.C. §103**

Claims 7 and 8 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Schatz (U.S. Patent No. 5,874,239) and further in view of Heda et al. (2000) *Biochem. Biophys. Res. Commun.* 271:659-664) for the reasons of record. The Examiner suggests that the specific biotin labeling as disclosed by Schatz is not a general incentive as argued by Applicants, it is an incentive specific to use of the biotin tag, and the tag is revealed by Schatz. It is

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further suggested that the combined teachings of Schatz and Heda et al. provide ample instruction and every expectation of success. The Examiner suggests that Heda et al. take advantage of the fact that glycosyl moieties are only present on the extracellular domains and extracellular loops to determine what amount of CFTR has been trafficked to the plasma membrane compared to the total present. It is suggested that one of skill in the art could easily determine from Heda et al. that the tag should go on an extracellular domain or loop. The Examiner further contends that Heda et al. do disclose the use of a permeabilizing agent and that limitations in the specification, as argued by Applicants, are not to be imported into the claims by the Examiner. Applicants respectfully traverse this rejection.

Under 35 U.S.C. §103, the factual inquiry into obviousness requires a determination of: (1) the scope and content of the prior art; (2) the differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) secondary considerations. *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966).

The Supreme Court has set forth that the reasoning for combining cited references should be explicit.

Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit. See *In re Kahn*, 441 F. 3d 977, 988 (CA Fed. 2006) ("[R]jections on obviousness grounds cannot be sustained by mere conclusory statements;

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instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness"). As our precedents make clear, however, the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.

In this regard, Applicants respectfully submit that the Examiner has not adequately explained how, based upon the mere suggestion by Schatz of biotin labeling membrane receptors, it can be reasonably concluded that insertion of a ~14-30 amino acid residue biotinylation peptide into an extracellular loop domain of a *misfolded mutant* membrane-localized protein, in and of itself, will not have an effect on the folding and membrane targeting of the protein. Indeed, Schatz only exemplifies biotin tagging at the *N-terminus* of *cytoplasmic* maltose binding protein (see column 12, lines 46-49, and Example 3). In so far as Heda et al. teach post-translational labeling of  $\Delta F508$  CFTR only *after* the protein has reached the plasma membrane (see paragraph spanning columns 1 and 2 at page 660), this reference does not compensate for the deficiencies in the teachings of the primary reference. As such, there is simply no basis for concluding that the primary sequence of the extracellular loop domain of a misfolded mutant membrane-localized protein can be disrupted by the insertion of a biotinylation peptide without having any effect on protein folding or transport through the secretory pathway.

"When the PTO shows prima facie obviousness, the burden then shifts to the applicant[s] to rebut." *In re Mayne*, 104 F.3d 1339, 1342, 41 USPQ2d 1451, 1454 (Fed. Cir. 1997). "Such rebuttal or

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argument can consist of a comparison of test data showing that the claimed compositions possess unexpectedly improved properties or properties that the prior art does not have..." *In re Dillon*, 919 F.2d 688, 692-93, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (en banc).

In this regard, Applicants have unexpectedly found that mislocalization of a misfolded mutant membrane-localized protein is preserved after insertion of a biotin target sequence into the extracellular loop domain of the protein (see page 10, lines 4-18). Such a finding cannot be inferred from the teachings of the cited prior art.

Moreover, Applicants respectfully disagree with the Examiner's suggestion that Heda et al. teach a permeabilizing agent. In so far as Office personnel must rely on Applicants' disclosure to properly determine the meaning of the terms used in the claims (*Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 980, 34 USPQ2d 1321, 1330 (Fed. Cir. 1995)), Heda et al. do not teach a permeabilizing agent in accordance with Applicants' disclosure at page 24, lines 23-30, or the conventional description of how such permeabilizing agents work. Applicants disclose at page 24 agents such as methanol, TRITON™ X-100, digitonin, and saponin to permeabilize cells. By way of illustration, Wikipedia describes saponin as a compound which is used to permeabilize or "make holes in" the plasma membrane *without destroying cell morphology* (see Wikipedia description of Saponin enclosed herewith). In contrast to this conventional description of how permeabilizing agents work, Heda et al. teach that "cells were lysed with 1% SDS" [emphasis added] to extracting cell lysate components (see the paragraph spanning columns 1 and 2 at page 660). Thus, the SDS of Heda et al. cannot be reasonably interpreted as a permeabilizing agent.

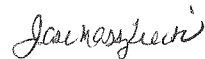
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Based on conclusions reached by the Examiner, it must be surmised that the only rationale for combining such disparate teachings in the manner proposed by the Examiner stems from an impermissible hindsight reconstruction of the Applicants' invention wherein the claims have been used as a template to selectively piece together isolated disclosures in the prior art. However, such a basis can not be used to establish a *prima facie* case of obviousness under 35 U.S.C. 103(a). It is therefore respectfully requested that this rejection be reconsidered and withdrawn.

### **III. Conclusion**

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,



Jane Massey Licata  
Registration No. 32,257

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Licata & Tyrrell P.C.  
66 E. Main Street  
Marlton, New Jersey 08053

(856) 810-1515